PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB 919 PCT	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/EP2005/002822	International filing date *(day/month/year)* 17.03.2005	Priority date *(day/month/year)* 25.03.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K31/18 A61K31/38 A61K31/4035 A61P25/00		
Applicant DOMPE' S.p.A.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.01.2006	26.06.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Cielen, E Telephone No. +31 70 340-4540

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/002822

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-4 as originally filed

   Drawings, Sheets

   1/4-4/4 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-4
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-4
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/EP2005/002822

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i. Reference is made to the following documents:

D1: EP-B-1 123 276 (DOMPE SPA) 16 August 2001 (2001-08-16)

D2: WO 02/062330 A (COLOTTA FRANCESCO ; NOVELLINI ROBERTO (IT); DOMPE SPA (IT); BERTINI RI) 15 August 2002 (2002-08-15)

D3: LI J J: "Small molecule interleukin-8 modulators" EXPERT OPINION ON THERAPEUTIC PATENTS 2001 UNITED KINGDOM, vol. 11, no. 12, 2001, pages 1905-1910, XP001079136 ISSN: 1354-3776

D4: SCHNELL L ET AL: "Neutrophil-mediated axonal damage in the adult rat spinal cord" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 2, 2001, page 1835, XP001199809 & 31ST ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE; SAN DIEGO, CALIFORNIA, USA; NOVEMBER 10-15, 2001 ISSN: 0190-5295

D5: XU J ET AL: "POLYMORPHONUCLEAR PMN CELL INFILTRATION IN EXPERIMENTAL SPINAL CORD INJURY" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 13, no. 3, 1987, page 1500, XP008034241 & 17TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, NEW ORLEANS, LOUISIANA, USA, NOVEMBER 16-21, 19 ISSN: 0190-5295

D6: ISAKSSON JONAS ET AL: "Expression of ICAM-1 and CD11b after experimental spinal cord injury in rats" JOURNAL OF NEUROTRAUMA, vol. 16, no. 2, February 1999 (1999-02), pages 165-173, XP008034243 ISSN: 0897-7151

D7: CALVILLO LAURA ET AL: "Reduction of ischemia-reperfusion injury in the rat in vivo by DF1681A, an inhibitor of interleukin-8" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 37, no. 2 Supplement A, February 2001 (2001-02), page 374A, XP001199808 & 50TH ANNUAL SCIENTIFIC SESSION OF THE AMERICAN COLLEGE OF CARDIOLOGY; ORLANDO, FLORIDA, USA; MARCH 18-21, 2001 ISSN: 0735-1097

D8: US 2001/016195 A1 (TOBINICK EDWARD L) 23 August 2001 (2001-08-23)

V.ii. Article 33(2) PCT.

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4 is new in the sense of Article 33(2) PCT. None of the prior art documents discloses the use of the presently claimed N-(2-aryl-propionyl)-sulfonamides for the treatment of spinal cord injury.

V.iii. Article 33(3) PCT.

(a) The problem to be solved by the present application is the provision of an (aspecific) inhibitor of the inflammatory response or of leukocyte recruitment for the treatment of spinal cord injury (description, p. 3, lines 21-23). The proposed solution is the use of N-(2-aryl-propionyl)-sulfonamides of formula (I).

(b) The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4 involves an inventive step in the sense of Article 33(3) PCT for the following reasons:

(1) Document D1 discloses that the presently claimed N-(2-aryl-propionyl)-sulfonamides are useful in the prevention and treatment of tissue damage due to the exacerbate recruitment of polymorphonuclear neutrophils (leukocytes PMN) at the inflammatory sites (p. 2, par-[0001]; p. 3, par. [0017] - p. 4, par. [0023]; p. 6, par. [0033]; claims 1-8, 10-12). The compounds are effective inhibitors of chemotaxis and degranulation of neutrophils with a remarkable degree of selectivity and specificity to IL-8-induced chemotaxis, as much higher concentrations are necessary to inhibit *in vitro* chemotaxis induced by other chemotactic factors. As IL-8 is involved in neutrophil infiltration in a number of pathologies, the compounds of D1 can be used in the treatment of these neutrophil-dependent pathologies (p. 3, par. [0016]; p. 6, par. [0039]; p. 7, par. [0045], [0048]). The compound of example 1 corresponds to present formula (II).

The subject-matter of claims 1-4 differs from D1 in that the same compounds are used for the treatment of an alternative neutrophil-dependent pathology, namely spinal cord injury.

From each of D4-D6, taken individually, it is known that neutrophil infiltration is involved in spinal cord injury (D4: whole document; D5: whole document; D6: abstract; p. 165, left-hand column, par. 1 - right-hand column, par. 1; p. 171, left-hand column, par. 2). However, these documents remain silent about the possible involvement of IL-8 in the neutrophil infiltration.

Moreover, the literature cited in the present application (description, p. 3, lines 4-17) indicates that several other inflammatory mediators also play a role in spinal cord injury.

In view of these teachings, the skilled person would rather look for an *aspecific* inhibitor of leucocyte recruitment to treat spinal cord injury.

D1 clearly mentions that the presently claimed compounds are *selective* inhibitors of IL-8 induced chemotaxis. Given this disclosure, the skilled person would not have expected that the presently claimed N-(2-aryl-propionyl)-sulfonamides would be effective in the treatment of spinal cord injury.

(2) The subject-matter of present claims 1-4 also involves an inventive step in the light of the combination of D8 with each of D2 or D7 for the following reasons:

Document D8 discloses that cytokine antagonists, which can be *inter alia* interleukin-8 antagonists, such as antibodies to IL-8, can be used for the treatment of acute spinal cord injury (par. [0002], [0019], [0029]-[0030], [0036]-[0040], [0052], [0066]-[0068]; claims 24, 25 and 28).

The subject-matter of present claims 1-4 differs herefrom in that alternative IL-8 antagonists are used for the same therapeutic application.

The problem to be solved by the present invention may therefore be regarded as the provision of alternative IL-8 inhibitors for the treatment of spinal cord injury.

Document D2 discloses that (R)-ibuprofen methanesulfonamide, which corresponds to present formula (II), and its lysine salt inhibit the biological activity of IL-8 (p. 2, lines 9-18; example 1, 2).

From D7, it is known that DF1681A, which corresponds to present formula II, is a non-protein IL-8 inhibitor.

It may therefore appear obvious for the person skilled in the art, knowing from D8 that IL-8 antagonists can be used for the treatment of spinal cord injury, and from each of D2 or D7 that the presently claimed N-(2-aryl-propionyl)-sulfonamides are IL-8 inhibitors, to at least try to use these compounds for the treatment of spinal cord injury with a reasonable expectation of success.

However, there is no direct connection in D8 between IL-8 inhibition and treatment of spinal cord injury. Claim 28 claims the administration of an IL blocker for treating acute spinal cord injury. According to the specification, this IL-8 blocker can be chosen out of seven different compounds, including a monoclonal antibody to IL-8, which is merely presented as one of the alternatives. Not only would the skilled person have to choose inhibition of IL-8 as a strategy to treat spinal cord injury, for which there is no hint in D8; he then would have to

replace the antibody to IL-8 by the presently claimed compounds. This was not obvious in view of the cited prior art.

(3) As far as the compound of formula (III) is concerned, this subject-matter appears inventive in the light of the cited prior art.

Even if this compound could be considered as a structural variant of the compounds disclosed in D1-D3 (D2: (p. 2, lines 9-18; example 1, 2; claims 1, 3, 4, 7, 8; D3: Abstract; p. 1905, par. 1; p. 1907, right-hand column, par. 2; compound 16) and D7, there was at the time of the invention no motivation or guidance to change the substituents of the compounds in D1-D3 or D7 in order to arrive at the compound of formula (III). Therefore, the person skilled in the art, upon reviewing D1-D3 and D7 would not be in a position to make the required changes necessary to obtain the compound of formula (III) usable for the treatment and management of spinal cord injury as claimed. Compound (III) is a non-obvious alternative over the prior art compounds; therefore, the subject-matter of present claim 4, as far as the compound of formula (III) is concerned, involves an inventive step.

(4) In the present application, protection from functional injury of spinal cord injury by the compounds of formula (II) and (III) has been demonstrated in an *in vivo* rat model (p. 5-10), in view of which it is credible that the problem underlying the application has been solved over the whole of the claimed scope.